

Applicants : Michael J. Elliott, et al.
U.S. Serial No: 08/602,272
Filed : February 16, 1996
Page 5

REMARKS

Claims 6, 8-10, 12-15, 29-32 and 34-37 are pending and under examination. By this Amendment applicants have amended claims 6, 9, 10, 12, 29, 31, 32 and 34; and canceled claims 8 and 30. Accordingly, upon entry of this Amendment claims 6, 9, 10, 12-15, 29, 31, 32 and 34-37 will be pending and under examination.

Support for the amendment to claim 6 is found, *inter alia*, on page 7, lines 9-10 and 27-29 of this application. Support for the amendment to claim 29 is found, *inter alia*, on page 6, lines 15-18; and page 7, lines 9-10 and 27-29 of this application. Claims 9, 10, 12, 31, 32 and 34 have been amended to remove dependencies on canceled claims 8 and 30.

Applicants maintain that these amendments to the claims do not raise any issue of new matter, and that these claims are fully supported by the specification as originally filed.

In view of the arguments set forth below, applicants maintain that the Examiner's rejections made in the September 12, 2005 Office Action have been overcome, and respectfully request that the Examiner reconsider and withdraw same.

The Claimed Invention

This invention provides methods of treating thrombosis, and decreasing plasma fibrinogen. These methods comprise administering an anti-TNF antibody or antigen binding fragment thereof to a subject diagnosed as suffering from thrombosis.

Applicants : Michael J. Elliott, et al.
U.S. Serial No: 08/602,272
Filed : February 16, 1996
Page 6

This invention is based on applicants' *surprising discovery* that inhibiting the biological activity of TNF α reduces fibrinogen levels in a subject. Since fibrinogen plays an integral role in forming thrombi, this invention has considerable use for treating thrombosis in subjects diagnosed as suffering from thrombosis.

Objection to Claim 15 Under 37 C.F.R. §1.75

The Examiner objected to claim 15 under 37 C.F.R. §1.75 as allegedly being a "substantial duplicate" of claim 14.

In response, applicants respectfully traverse. Claim 15 is drawn to a method employing a chimeric antibody that competitively inhibits binding of TNF α to monoclonal antibody cA2, wherein claim 14 is drawn to a method employing the monoclonal antibody cA2. Accordingly, claims 15 and 14 are not of the same scope, and thus are not "substantial duplicates" of one another.

In view of the above remarks, applicants maintain that claims 14 and 15 satisfy the requirements of 37 C.F.R. §1.75.

Rejection Under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 6, 8-10 and 12-15 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to point out and distinctly claim the subject matter which applicants regard as the invention. Specifically, the Examiner alleged that the limitation "preventing thrombosis in a

Applicants : Michael J. Elliott, et al.
U.S. Serial No: 08/602,272
Filed : February 16, 1996
Page 7

subject diagnosed as suffering from thrombosis" is indefinite since it is unclear how thrombosis can be "prevented" when a subject is already suffering from thrombosis.

Regarding the rejection of claim 8, applicants point out that this claim has been cancelled, making the rejection thereof moot.

In response to the Examiner's rejection of the remaining claims, and without conceding the correctness thereof, applicants note that amended claims 6, 9, 10 and 12-14 do not recite the term "preventing."

In view of the above remarks, applicants maintain that claims 6, 9, 10 and 12-14 satisfy the requirements of 35 U.S.C. §112, second paragraph.

Rejection Under 35 U.S.C. §112, First Paragraph - Written Description

The Examiner rejected claims 6, 8-10, 12-15, 29-32 and 34-37 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Examiner acknowledged that the instant claims have been amended to incorporate the limitation of "a subject diagnosed as suffering from thrombosis." The Examiner alleged that the specification and the claims, as filed, are drawn to the treatment of thromboembolic disorders, where the thromboembolic disorder includes deep vein thrombosis. The Examiner alleged that neither the specification nor the claims, as filed, provide support for limiting treatment to

Applicants : Michael J. Elliott, et al.
U.S. Serial No: 08/602,272
Filed : February 16, 1996
Page 8

subjects "diagnosed" as suffering from thrombosis. The Examiner further alleged that neither the specification nor the claims, as filed, provide support for the treatment of thrombosis, nor for the method of decreasing the level of plasma fibrinogen in a subject diagnosed with thrombosis.

Regarding the rejection of claim 8, applicants point out that this claim has been cancelled, making the rejection thereof moot.

In response to the Examiner's rejection of the remaining claims, applicants respectfully traverse. Applicants point out that the subject specification provides support for both treating thrombosis and decreasing the level of plasma fibrinogen in a subject diagnosed with thrombosis. To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. The subject specification indicates both that plasma fibrinogen levels can be controlled and thrombotic disorders treated through long term blockade of TNF. The specification also discloses, as noted on page 6, lines 2-9, that a "thrombotic disorder" is a condition where *thrombosis* is a pathogenic component. The specification further discloses, on page 6, lines 19-20, that the present invention can be used to treat *thrombosis*. Based on the subject disclosure, those skilled in the art would recognize that plasma fibrinogen levels can be controlled and thrombosis treated in an individual by the same method, i.e., the long term blockade of TNF.

Applicants : Michael J. Elliott, et al.
U.S. Serial No: 08/602,272
Filed : February 16, 1996
Page 9

Since applicants were in possession of a method of controlling plasma fibrinogen and treating thrombosis in an individual, those skilled in the art would recognize that these methods would necessarily be used on individuals diagnosed as suffering from thrombosis. Therefore, those skilled in the art can conclude, from the subject disclosure, that applicants were in possession of methods of treating thrombosis and decreasing the level of plasma fibrinogen in an individual diagnosed as suffering from thrombosis.

In view of the above remarks, applicants maintain that claims 6, 9, 10 and 12-14 satisfy the written description requirements of 35 U.S.C. §112, first paragraph.

Rejections Under 35 U.S.C. §102(b)

The Examiner rejected claims 6 and 29 under 35 U.S.C. §102(b), as allegedly anticipated by the abstract of Martini, et al. (Current Therapeutic Research, 1993, Vol. 53, pp. 340-346), or the abstract of Di Perry, et al. (Haemostasis, 1986, Vol. 16, Suppl. 1, pp. 42-47), both as evidenced by Bianchi, et al. (European Journal of Pharmacology, 1993, Vol. 238, pp. 327-334).

In response, applicants respectfully traverse. Applicants note that claims 6 and 29, as amended, are directed to methods comprising administering an anti-tumor necrosis factor antibody or antigen-binding fragment thereof. None of the cited references discloses such element. Accordingly, none of the cited references recites each and every element of either of the rejected claims.

Applicants : Michael J. Elliott, et al.
U.S. Serial No: 08/602,272
Filed : February 16, 1996
Page 10

The Examiner also rejected claims 6 and 29 under 35 U.S.C. §102(b), as allegedly anticipated by the abstract of Mozzi, et al. (Haemostasis, 1986, Vol. 16, Suppl. 1, pp. 36-38), or the abstract of Ciavarella, et al. (Haemostasis, 1986, Vol. 16, Suppl. 1, pp. 39-41), both as evidenced by Bianchi, et al. (European Journal of Pharmacology, 1993, Vol. 238, pp. 327-334).

In response, applicants respectfully traverse. Applicants again note that claims 6 and 29, as amended, are directed to methods comprising administering an anti-tumor necrosis factor antibody or antigen-binding fragment thereof. None of the cited references discloses such element. Accordingly, none of the cited references recites each and every element of either of the rejected claims.

In view of the above remarks, applicants maintain that claims 6 and 29 satisfy the requirements of 35 U.S.C. §102(b).

Rejections Under 35 U.S.C. §103(a)

The Examiner rejected claims 6, 8-10 and 12-15 under 35 U.S.C. §103(a), as allegedly unpatentable over Creager, et al. ('Vascular Diseases of the Extremities', in: Harrison's Principles of Internal Medicine, 13th Ed. Vol. 1, Isselbacher et al. Eds., pp. 1135-1142) in view of Le, et al. (PCT International Application No. WO 92/16553).

Regarding the rejection of claim 8, applicants point out that this claim has been cancelled, making the rejection thereof

Applicants : Michael J. Elliott, et al.
U.S. Serial No: 08/602,272
Filed : February 16, 1996
Page 11

moot.

In response to the Examiner's rejection of the remaining claims, applicants respectfully traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness.

Amended claims 6, 9, 10, and 12-15 provide methods of treating thrombosis comprising administering a therapeutically effective amount of an anti-tumor necrosis factor antibody or antigen-binding fragment thereof to a subject diagnosed as suffering from thrombosis.

To establish a *prima facie* case of obviousness, the Examiner must demonstrate three things with respect to each claim. First, the cited references, when combined, must teach or suggest every limitation of the claims. Second, one of ordinary skill would have been motivated to combine the teachings of the cited references at the time of the invention. And third, there would have been a reasonable expectation that the claimed invention would succeed.

Here, to support a *prima facie* case of obviousness, the combined teachings of Creager, et al. and Le, et al., at the time of the invention, would have to provide a reasonable expectation of success.

Creager, et al. and Le, et al. fail to do this.

Again this invention is based on the *surprising finding* that inhibiting the biological activity of TNF α reduces fibrinogen

Applicants : Michael J. Elliott, et al.
U.S. Serial No: 08/602,272
Filed : February 16, 1996
Page 12

levels in a subject.

Creager, et al. teaches a method for preventing pulmonary embolism by administering anticoagulants to patients with deep vein thrombosis. This reference does not teach that anticoagulants decrease plasma fibrinogen levels in an individual diagnosed as suffering from thrombosis.

Le, et al. fails to cure the deficiencies of Creager, et al. This reference does not teach or suggest applicants' underlying discovery, nor does it teach or suggest the treatment of thrombosis, or decreasing the levels of plasma fibrinogen in a subject diagnosed as suffering from thrombosis. Indeed, Le, et al. does not even mention the terms "thrombosis" or "plasma fibrinogen."

In light of these teachings and their shortcomings, the Examiner has failed to show that the cited references together present a motive to combine or a reasonable expectation of success. To maintain otherwise would be hindsight.

Accordingly, the Examiner has failed to establish the *prima facie* obviousness of claims 6, 9, 10 and 12-15 over Creager, et al. and Le, et al.

The Examiner also rejected claims 29-32 and 34-37 under 35 U.S.C. §103(a), as allegedly unpatentable over Creager, et al. in view of Le, et al. as evidenced by Charles, et al. (*Journal of Immunology*, 1999, Vol. 163, pp. 1521-1528).

Regarding the rejection of claim 30, applicants point out that

Applicants : Michael J. Elliott, et al.
U.S. Serial No: 08/602,272
Filed : February 16, 1996
Page 13

this claim has been cancelled, making the rejection thereof moot.

In response to the Examiner's rejection of the remaining claims, applicants respectfully traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness.

Amended claims 29, 31, 32 and 34-37 provide methods of decreasing plasma fibrinogen comprising administering a therapeutically effective amount of an anti-tumor necrosis factor antibody or antigen-binding fragment thereof to a subject diagnosed as suffering from thrombosis.

Here, to support a *prima facie* case of obviousness, the teachings of Creager, et al., Le, et al. and Charles, et al. would have to provide a reasonable expectation of success.

They fail to do this.

The teachings of Creager, et al. and Le, et al. are discussed above, as is applicants' discovery underlying this invention. Again, applicants maintain that, *inter alia*, these two references fail to create a reasonable expectation of success or motive to combine.

The Examiner acknowledges that neither Le, et al. nor Creager, et al. teaches a decrease in serum fibrinogen levels. However, the Examiner alleges that it would be inherent in the method of administering cA2 antibody that serum fibrinogen levels would decrease as evidenced by Charles, et al.

Applicants : Michael J. Elliott, et al.
U.S. Serial No: 08/602,272
Filed : February 16, 1996
Page 14

Charles, et al., which was published after the filing date of the subject application, does nothing to negate the nonobviousness of the claimed method. That is, absent a motive to combine or expectation of success at the time of filing (which did not exist absent applicants' discovery), the Examiner's subsequent evidence as to "inherency" cannot properly serve as evidence of obviousness.

In view of the above, the Examiner has failed to show that the cited references present a motive to combine or a reasonable expectation of success.

Accordingly, the Examiner has failed to establish the *prima facie* obviousness of claims 29, 31, 32 and 34-37 over Creager, et al. and Le, et al. in view of Charles, et al.

Provisional Obviousness-Type Double Patenting

The Examiner provisionally rejected claims 6, 8-10 and 12-15 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-34 of a co-pending application (inadvertently unidentified by the Examiner) in view of Creager, et al. and Le, et al.

Again, claim 8 has been cancelled, rendering the provisional rejection thereof moot.

In response to the provisional rejection of the remaining claims, applicants note that, should this rejection become non-provisional and once the Examiner identifies the

Applicants : Michael J. Elliott, et al.
U.S. Serial No: 08/602,272
Filed : February 16, 1996
Page 15

application on which this rejection is based, applicants will either traverse the rejection and set forth their grounds for doing so, or will file a terminal disclaimer, whichever action is deemed appropriate.

Summary

In view of the foregoing remarks, applicants respectfully request that the above grounds of rejection be reconsidered and withdrawn and earnestly solicit allowance of the pending claims.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

Applicants : Michael J. Elliott, et al.
U.S. Serial No: 08/602,272
Filed : February 16, 1996
Page 16

No fee is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Alan J. Morrison
Reg. No. 37,399

12/12/01
Date

John P. White
Registration No. 28,678
Alan J. Morrison
Registration No. 37,399
Attorneys for Applicants
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036
Tel. No. (212) 278-0400